

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re:	Application No. 10/596,209	)	<i>Confirmation No. 3439</i>
Filed:	June 2, 2006	)	
Applicants:	Nanping ZHONG et al.	)	
Title:	METHOD FOR THE ENANTIOMERIC SEPARATION OF OPTICAL ACTIVE AMLODIPINE	)	This Amendment was electronically filed on July 6, 2009 using the USPTO's EFS-Web.
Art Unit:	1625	)	
Examiner:	Davis	)	
Attorney Docket:	8378/88501	)	
Customer No.:	22242	)	

Commissioner for Patents  
P. O. Box 1450  
Alexandria, Virginia 22313-1450

**AMENDMENT A**

Sir:

In response to the office action dated April 6, 2009, please amend this application as follows:

**Amendments to the Claims** begin on page 2 of this paper.

**Remarks** begin on page 5 of this paper.

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**LISTING OF CLAIMS:**

1. (currently amended) A method for preparing (S)-(-)-amlodipine comprising: comprising dissolving racemic amlodipine and L-(+)-tartaric acid in an organic solvent containing 2-butanone to yield (S)-(-)-amlodipine-L-(+)-tartrate precipitate by reaction; separating the precipitate; recrystallizing the precipitate by using a lower alcohol solvent to obtain a solid; adding a lower alkyl halide into the solid; and neutralizing with the resulting solution is neutralized by an aqueous alkali to give (S)-(-)-amlodipine.

2. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein said organic solvent is 2-butanone or mixture of 2-butanone with a cosolvent.

3. (Original) The method for preparing (S)-(-)-amlodipine according to claim 2, wherein said cosolvent is selected from the group consisting of methanol, ethanol, n-butanol, acetone, 2-pentanone, ethyl ether, methyl ethyl ether, ethyl acetate, ethyl formate, dichloromethane and chloroform.

4. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein the molar ratio of racemic amlodipine to L-(+)-tartaric acid is 1:0.25~0.8.

5. (Original) The method for preparing (S)-(-)-amlodipine according to claim 4, wherein the molar ratio of racemic amlodipine to L-(+)-tartaric acid is 1:0.5.

6. (Original) The method for preparing (S)-(-)-amlodipine according to claim 1, wherein said lower alcohol solvent is selected from the group consisting of ethanol, methanol and isopropanol.

7. (currently amended) A method for preparing (R)-(+)-amlodipine comprising; ~~comprises~~ dissolving racemic amlodipine and D-(-)-tartaric acid in an organic solvent containing 2-butanone to yield (R)-(+)-amlodipine-D-(-)-tartrate precipitate by reaction; separating the precipitate; recrystallizing the precipitate by using a lower alcohol solvent to obtain a solid; adding a lower alkyl halide into the solid; and neutralizing with the resulting solution is neutralized by an aqueous alkali to give (R)-(+)-amlodipine.

8. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein said organic solvent is 2-butanone or mixture of 2-butanone with a cosolvent.

9. (Original) The method for preparing (R)-(+)-amlodipine according to claim 8, wherein said cosolvent is selected from the group consisting of methanol, ethanol, n-butanol, acetone, 2-pentanone, ethyl ether, methyl ethyl ether, ethyl acetate, ethyl formate, dichloromethane and chloroform.

10. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein the molar ratio of racemic amlodipine to D-(-)-tartaric acid is 1:0.25~0.8.

11. (Original) The method for preparing (R)-(+)-amlodipine according to claim 10, wherein the molar ratio of racemic amlodipine to D-(-)-tartaric acid is 1:0.5.

12. (Original) The method for preparing (R)-(+)-amlodipine according to claim 7, wherein said lower alcohol solvent is selected from the group consisting of ethanol, methanol and isopropanol.

## REMARKS

Claims 1-12 remain in this application.

### Rejections under 35 USC 103

The presently claimed process actually is substantively different from the process of D1 at least in the following aspects.

1) D- or L-tartaric acid, (R,S)-amlodipine and DMSO form a DMSO-solvate precipitate in D1, i.e., DMSO is a part of the solvate precipitate (see D1, especially the Examples), while D- or L-tartaric acid and (R,S)-amlodipine form a tartrate salt precipitate (not a solvate) in 2-butanone in the present invention. i.e., 2-butanone is not a part of the salt precipitate. Thus, DMSO is not only a solvent but also a reagent in D1, while 2-butanone is only a solvent in the present invention. Therefore, DMSO in the solvate precipitate may have to be removed by using other solvent, such as refluxing methanol in D1, while a solvent-free tartrate salt precipitate could be directly obtained by filtration in the present invention.

2) In addition, D-tartaric acid is used to obtain (S)-(-)-amlodipine (see D1, Examples 1-4) and L-tartaric acid is used to obtain (R)-(+)-amlodipine (see D1, Examples 5-8) in D1. On the contrary, L-tartaric acid is used to obtain (S)-(-)-amlodipine and D-tartaric acid is used to obtain (R)-(+)-amlodipine in the present invention. Thus, the reaction employed in D1 is different from the reaction of the present invention.

3) D1 discloses that the e.e. values of the obtained (S)-(-)-amlodipine and (R)-(+)-amlodipine are 98.4% and 98.5%, respectively (see Examples 3 and 8). In the present invention, the e.e. values of the obtained (S)-(-)-amlodipine and (R)-(+)-amlodipine are 99.0% and 98.8%, respectively (see Examples 1 and 2). Hence, the presently claimed process could reach higher e.e. value in comparison with D1.

4) According to the material safety data sheets of DMSO and 2-butanone (see the attached documents), DMSO has a boiling point of 189°C and an explosion limits of 3.5-42% and 2-butanone has a boiling point of 79-80°C and an explosion limits of 1.8-10%, which means higher cost is needed to use and recover DMSO in view of safety and energy consumption in comparison with 2-butanone.

In view of the above discussion, D1 does not provide any teaching, suggestion or motivation to adopt the presently claimed process for producing enantiomers of amlodipine in industrial scale. D2 merely indicates that DMSO and 2-butanone are Class 3 solvents in view of their toxicity, but does not provide any information about using them in the separation of enantiomers of amlodipine. Hence, those skilled in the art would not obviously obtain the presently claimed process based on D1 and D2. Therefore, the pending claims 1-12 are non-obvious over D1 in view of D2 and Applicant respectfully requests allowance of those claims.

The Commissioner is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 06-1135.

Respectfully submitted,  
FITCH, EVEN, TABIN & FLANNERY

Dated: JUL 06 2009

  
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## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	5643417
<b>Application Number:</b>	10596209
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	3439
<b>Title of Invention:</b>	Method for the enantioselective separation of optical active amlodipine
<b>First Named Inventor/Applicant Name:</b>	Nanping Zhong
<b>Customer Number:</b>	22242
<b>Filer:</b>	James P. Krueger/Jackeline Torres
<b>Filer Authorized By:</b>	James P. Krueger
<b>Attorney Docket Number:</b>	8378/88501
<b>Receipt Date:</b>	06-JUL-2009
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<b>Time Stamp:</b>	11:16:40
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### File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part/.zip	Pages (if appl.)
1		88501_AmendmentA_07062009.pdf	194465 c488b1a1a095994d19e77c2db5b63158 86a9e2	yes	6

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Amendment/Req. Reconsideration-After Non-Final Reject	1	1	
Claims	2	4	
Applicant Arguments/Remarks Made in an Amendment	5	6	

**Warnings:**

**Information:**

Total Files Size (in bytes):	194465
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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PATENT APPLICATION FEE DETERMINATION RECORD				Application or Docket Number 10/596,209	Filing Date 06/02/2006	<input type="checkbox"/> To be Mailed
Substitute for Form PTO-875						
APPLICATION AS FILED – PART I						
(Column 1)		(Column 2)		SMALL ENTITY <input type="checkbox"/>		OTHER THAN SMALL ENTITY
FOR	NUMBER FILED	NUMBER EXTRA		RATE (\$)	FEES (\$)	
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A		N/A
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(b), (f), or (m))	N/A	N/A		N/A		N/A
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(c), (g), or (j))	N/A	N/A		N/A		N/A
TOTAL CLAIMS (37 CFR 1.16(j))	minus 20 =	*		X \$ =		OR
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		X \$ =		
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(e))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).					
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))						
				TOTAL		TOTAL
* If the difference in column 1 is less than zero, enter "0" in column 2.						
APPLICATION AS AMENDED – PART II						
(Column 1)		(Column 2)		(Column 3)		OTHER THAN SMALL ENTITY
AMENDMENT	07/06/2009	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	SMALL ENTITY	OR
Total (37 CFR 1.16(h))	* 12	Minus	** 20	= 0	RATE (\$)	ADDITIONAL FEE (\$)
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X \$ =	OR X \$52= 0
<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))				X \$ =	OR X \$220= 0	
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR	
				TOTAL ADD'L FEE	OR	TOTAL ADD'L FEE 0
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)
Total (37 CFR 1.16(h))	* 12	Minus	** 20	= 0	X \$ =	OR X \$ =
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X \$ =	OR X \$ =
<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))					OR	
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					OR	
				TOTAL ADD'L FEE	OR	TOTAL ADD'L FEE

\* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

\*\* If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

\*\*\* If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Legal Instrument Examiner:  
/JOSEPH BROOKS/